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Review Article

Diagnosis and treatment of novel Coronavirus 2019 (COVID-19): A comprehensive review of the current literature

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Abstract

Coronavirus disease 2019 (COVID-19) is a pandemic caused by the novel coronavirus 2019. The rapid deployment of effective therapeutics is a high priority for researchers as there is still no specific medication and vaccine to treat the disease. Researchers worldwide are working and sharing their contribution regarding epidemiology, prevention, treatment, clinical and diagnostic patterns of the COVID-19. Current review is another contribution to the current literature, presenting the diagnosing techniques, effectiveness of medications that could be most appropriate therapeutic options for patients of SARS-CoV-2.

Keywords: Coronavirus disease 2019; Diagnosis; Medications

Introduction

In late December 2019, the 2019 novel coronavirus (2019-nCoV) was discovered, On January 30, 2020 the World Health Organization (WHO) declared COVID-19 pandemic, a Public Health Emergency of International Concern (PHEIC). Coronaviruses belongs to coronavirus genus in the Coronaviridae family. All coronaviruses have single stranded Ribonucleic acid (RNA), crown shape peplomers (80-160 nM in size) **[1, 2]**. The mutation rate is high in coronaviruses due to RNA Dependent RNA Polymerase (RdRP) jumps and constantly developing transcription errors. Due to their high mutation rate and fast transmission, with wide range of clinical features from asymptomatic to symptomatic state make lethal infection worldwide, which usually cause infections in respiratory, gastrointestinal, hepatic and neurologic systems **[3]**.

Earlier, coronaviruses three epidemic episodes has been reported, (1) sever acute respiratory syndrome (SARS) coronavirus, that had a little impact on global mortality and morbidity with more than 774 deaths, (2) Middle East respira- tory syndrome (MERS)-coronavirus, that had originated in Saudi Arabia, (3) the SARS-CoV-2, that appears in December 2019, spread out pandemic, infected more than 19,718,030 individuals and died 728,013, still the outbreak is not controlled [4].

SARS-CoV-2, have been defined as a novel respiratory track virus found in the sample collection from infected individuals [5]. Coronaviruses have a large family that are found in different animals such as cattle, camels, bats and cats however animal viruses, rare to infect humans. However, palm cats have been proposed to be natural reservoir of human coronaviruses and camels for MERS [6]. According to current literature studies that bats are natural host of both MERS-CoV and SARS-CoV. Studies shows that alpha-CoV and beta-CoVs, genes are the source of bat CoVs, while gamma-CoVs and delta-CoVs are birds CoVs [3].

The rapid deployment of effective therapeutics is a high priority for researchers as there is still no specific medication and vaccine to treat the disease. Treatment of SARS-CoV-2 is still a challenge however there are several general treatment methods used to treat the lethal disease. The clinical use of ribavirin with and without corticosteroids, ribavirin with lopinavir and ritonavir, interferon alfa with corticosteroids and convalescent plasma may improve the outcome in patients [7]. The purpose of current literature review is to summarize the different diagnosing techniques, effectiveness of medications and to identify therapeutic approach that could be most appropriate therapeutic options for patients of SARS-CoV-2.

Clinical diagnosis of COVID-19

COVID-19 clinical diagnosis consists on physical examination, CT/Xray imaging, and viral nucleic acid detection other rapid diagnosing techniques are based on blood culture and immune identification such as enzyme-linked immunosorbent assay (ELISA) and Point-of-care Testing (POCT) of IgM/IgG.

Physical examination

COVID-19 infected patients' clinical signs and symptoms are fever, cough, dyspnea, viral pneumonia, dullness in percussion, varying in tactile speech tremor. Patients with severe conditions may have symptoms such as shortness of breath, moist rales in lungs and weakened breath sounds. However, according to literature, fever is the most typical symptom for COVID-19 infection.

Nucleic acid detection technology

CoV nucleic acid detected through real time quantitative polymerase chain reaction (RT-qPCR) and high throughput sequencing method. Specimens for viral nucleic acid detection purpose can be collected from trachea or nasopharynx extract, nasal swabs, sputum, lung tissue, blood and feces should be retained from patients. High throughput sequencing and virus blood culture are the most accurate method of diagnosis however its application is limited due to high cost and equipment dependency. RT-qPCR is a simple and effective method most commonly used for viral nucleic acid detection for blood and respiratory specimens. After SARS-CoV-2 outbreak, Chinese companies launched RT-qPCR test kits, approved by Chinese Center for Disease Control and Prevention (China CDC) [4, 8]. Other rapid diagnosis kits are also available based on targeted antibodies or antigens such as ELISA and POCTof IgM/IgG kits have been developed and have higher detection rate [9].

CT imaging examination

CT imaging of lungs is an important technique for detection purposes, clinicians

proposed CT imaging, particularly for false negative results of RT-qPCR method [4]. CT scan results vary with drug intervention, immunization status, underlying disease and disease at stage of scanning. Disease at initial stage, chest X-ray shows small patchy shadows however in severe condition, infiltrating shadow and pulmonary consolidation (with infrequent pleural effusion) [2, 10]. Pulmonary lesions are more clearly shown in CT scan than X-ray image as well as segmental consolidation and ground glass opacity in bilateral lungs while in children's (severe infection) in both lungs multiple lobar lesions may be present [9, 11].

Treatment of COVID-19

At the present moment there is no specific treatment for Covid-19 and therefore the WHO (2020) has launched a solidarity clinical trial in order to face the current scenario where 5-10% of the patients have life threatening situation [12]. Following are the list of medications that are being under clinical trial for treatment of COVID-19 disease.

Remdesivir

Remdesivir also known as GS-5734 is an antiviral agent that was designed for the treatment of Ebola and Marburg disease. This drug is a prodrug and when it metabolizes in the body then it makes a nucleotide analogue that is adenosine triphosphate that targets the viral Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) polymerase [13]. Remdesivir was found to have no toxicity in the human body because this drug selectively targets the polymerases and therefor only targets the viral polymerase [14]. The first case of Covid-19 which was reported to be treated with Remdesivir was a 35 years old male in the United States that person did not show any adverse reaction against Remdesivir [15] along with that two other patients were also treated with Remdesivir and they were recovering finely. The current dose of Remdesivir which is under investigation is 200 mg on the first day which is administered intravenously followed by 100 mg for ten days [13].

Lopinavir/ritonavir

Lopinavir/ritonavir both are used to control the human immunodeficiency virus (HIV) infection where ritonavir act as a booster. Lopinavir/ritonavir both are protease inhibitors and they both are used in equal combination. This enzyme (protease) is required for the processing of polyprotein required for the replication of virus (2). Inhibition of this enzyme causes inhibition of viral replication [13]. According to one of studies conducted by Young et al in first 18 patients in Singapore. In which 5 patients were receiving Lopinavir/ritonavir. Out of which 3 patients had decreased in the requirement of oxygen and 2 patients died due to respiratory failure. 2 patients had clearance of viral shedding upon treatment while four patients couldn't complete the 14 days treatment course due to adverse events [16]. Different case reports were also published from Korea and China, but the data couldn't be interpreting properly due to inclusion of other therapies along with Lopinavir/ritonavir such as corticosteroids [17-19].

According to one of the studies conducted by Cao et al when the group of patients receiving Lopinavir/ritonavir were compared with the patients receiving standard care then no difference was found. Total number of patients that were kept under observation were 199. In which 100 were receiving standard care while 99 were receiving Lopinavir/ritonavir. Mortality rate at 28 days were similar in both standard care and lopinavir/ritonavir group. The mortality rate of standard care and lopinavir/ritonavir group were 19.2% vs 25.0%. Viral RNA at various points were also similar [20].

Nucleoside analogues

Nucleoside analogues are antimetabolites which are evaluated through clinical trials in

recent years [21]. These therapeutic compounds can imitate the nucleosides which are present in the body and thus once incorporated in DNA during DNA synthesis then it leads to synthesis inhibition or chain termination. These compounds also inhibit enzymes which are involved in making of purines and pyrimidines and RNA synthesis. These all events lead to cell death ultimately [22]. The examples of nucleoside analogues are favipiravir, ribavirin and remdesivir etc. The nucleoside analogues which are under clinical trial for Covid-19 is ribavirin and remdesivir. Ribavirin is a guanine analogue which has been used for the treatment of hepatitis C and previous corona virus disease like SARS and MERS [23] but there are certain side effects as well such as anemia. Ribavirin has been used in lower doses with the combination of pegylated interferons to stimulate the immune system for Covid-19 [24]. This drug is found to be effective against Covid-19 in-Vitro and targets RNA dependent RNA polymerase according to molecular data [25].

Remdesivir is an adenine nucleoside which was designed for Ebola and is under phase III clinical trial for Covid-19 [26]. This drug showed activity against SARS and MERS in-Vitro and in mice [27]. This drug is found to improve lung function and reduces viral loads [25].

Neuraminidase inhibitor

There is no data suggesting the use of neuraminidase inhibitory agents for Covid-19 because this virus don't utilize neuraminidase and therefor there is no any enzyme which is inhibited by these inhibitors. Oseltamivir which is a neuraminidase inhibitory molecule has been approved for influenza A and B treatment. This drug inhibits the release of viral particles from host cell by blocking the neuraminidase of virus (20). Oseltamivir and baloxavir both have antiviral activity against influenza. But once influenza has been ruled out then these agents should be avoided for Covid-19. There is no any mechanism or data suggesting the use of neuraminidase inhibitors in coronavirus patients [13].

Corticosteroid therapy

Lung infection causes inflammation of lungs which cause injury of lungs and therefor to prevent from lung inflammation corticosteroid therapy is used but its use also increases the risk of secondary infection which increases the timing of cleansing of virus. Use of corticosteroid for patients of corona is not clear because different analysis shows different results [26]. According to one of data use of corticosteroid has decreased the mortality rate in critically ill patients [27] while in others worst outcome has been seen with the patients receiving steroids and even delayed the clearance of virus [28]. According to a recent data decrease in the rate of mortality has been seen in SARS-CoV-2 patients who were receiving corticosteroids suggested a decrease in mortality in patients with ARDS with the receipt of corticosteroids [18].Careful consideration is required for the dosage of corticosteroid for Covid-19 and the ratio of risk and benefit should be checked for each individual patient. According to a statement from Chinese Thoracic Society a lower dose of ≤0.5–1 mg/kg/day of methylprednisolone for ≤7 days is prescribed in selected patients by measuring the ratio of risk and benefit [29].

Peptide (EK1)

The HCoVs enters host cell through its S protein. This S protein is transmembrane glycoprotein and is common in all human coronavirus. This S protein consist of two subunits: S1 and S2. This virus binds with host membrane through RBD (receptor binding domain) of S1 resulting conformational change in S2 and fusion peptide is inserted into host cell membrane. S2 subunit contain heptad repeat 1 (HR1) and heptad repeat 2 (HR2). The HR1 region of S2

subunit forms a homotrimeric assembly and exposes three grooves on the surface which are highly conserved and hydrophobic. Thus, it fuses with HR2 through these grooves. This fusion results in six helix bundle formation (6-HB) and brings the host and viral membrane into close contact for virus entry **[30]**. Therefor this S protein is an important target protein for drug development to inhibit virus entry into host cell. The RBD of S1 subunit can be used as a target site for both antibodies and vaccine development to prevent from binding of virus with host cell membrane **[31]**. But this part of CoV is highly mutable and therefor can't be used as an ideal target site for broad spectrum antiviral drug development **[31]**. In contrast to this the HR region of S2 subunit is highly conserved among HCoV and mediates the binding of virus and host membrane by forming 6-HB. Previous studies show that peptides from HR2 region binds with HR1 region and inhibit viral infection. These peptides can be used to inhibit 6-HB formation and prevent from fusion of host and viral membranes. Such peptide is OC43-HR2P which has a broad- spectrum activity. A modified form of OC43-HR2P is EK1 which has more promising results. In Vivo studies show that when EK1 is administered through nasal route then it has more protective effect **[32]**.

Arbitol

Arbitol is a broad-spectrum antiviral drug that has been used for influenza **[33]** and made in Russian Research Chemical-Pharmaceutical Institute **[34]**. It is licensed in both China and Russia for respiratory infections **[33]**. It inhibits the entry of virus inside host cell by blocking the fusion of virus with host membrane **[35]**. Its antiviral activity has also been reported in hepatitis B and C virus **[36]**. A clinical pilot trial was conducted in Wuhan, China in January 2012 where 67 COVID-19 patients were kept under observation in which 36 patients received umifenovir (arbitol) of 400 mg three times a day for 9 consecutive days while 31 patients served as a control group and remained un-treated. In this trial a decrease in mortality was observed (16% vs 0%) in arbitol treated and control group **[37]**. Another study was conducted in February 2020 in Guangdong, China. In which a total of 33 COVID-19 patients were kept under observation. In which 16 patients received 200 mg of umifenovir after every 8 h and 400 mg of lopinavir and 100 mg of ritonavir every 12 h for 5-21 days consecutively while 17 patients served as control group and only received lopinavir and ritonavir of 400 mg and 100 mg respectively after every 12 h. After 14 days of treatment when COVID-19 patients were detected through RT-PCR then 94 % vs. 53 % of COVID-19 patients' results were negative as compare to control group **[38, 39]**.

Antibiotic medications

Teicoplanin is a glycopeptide antibiotic which has been used for the bacterial infections caused by Gram positive bacteria such as, streptococcus and staphylococcus bacteria **[40]**. This antibiotic has also found to be effective against n-CoV. The entry of virus into host cell requires binding of host cell membrane with viral membrane and for that sequential cleavage of S protein of corona virus with TMPRSS2 and cathepsin L is required [41]. The virus first binds with the host cell through its S protein by binding with ACE2 which is present on the surface of cell. Binding of S protein with ACE2 cause conformational change in S protein and cause activation of TMPRSS1 **[40, 42]** then through process of endocytosis the virus enters early cell endosome and further cleaves by cathepsin L in late endosome **[41]**. This teicoplanin has found to have potential to prevent from n-CoV to inhibit the enzymatic activity of cathepsin L that is required for S protein activation for viral entry **[43]**.

Conclusion

Current research review based on diagnosis and therapeutics use to treat COVID-19 disease. For diagnosis purpose, RT-qPCR and CT scan are best suitable techniques, however there is no specific antiviral treatment available for this pandemic disease and clinical trials are going on in different regions of the world. Therefor looking towards the current scenario, the best, we can do is to protect yourself from exposure to this virus by following the safety measures given by WHO 2020.

Authors' contributions

Conceived and designed the experiments: H Ullah & A Gull, Performed the experiments: N Iqbal & A Ullah, Analyzed the data: NM Khan & A Raziq, Wrote the paper: H Ullah and A Gull.

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